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Effect of Food Intake on Pharmacokinetics of Oral Artemisinin in Healthy Vietnamese Subjects

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The influence of food intake on the pharmacokinetics of artemisinin was studied with six healthy Vietnamese male subjects. In a crossover study, artemisinin capsules (500 mg) were administered with and without food after an overnight fast. Plasma samples were obtained up to 24 h after intake of each drug. Measurement of artemisinin concentrations was performed by high-performance liquid chromatography with electrochemical detection. Tolerance was evaluated according to subjective and objective findings, including repeated physical examinations, routine blood investigations, and electrocardiograms. Pharmacokinetics were analyzed with a noncompartmental method and with a one-compartment model. This model had either zero-order or first-order input. No statistically significant differences were found between the results of the two experimental conditions. Specifically, there were no consistent differences in parameters most likely to be affected by food intake, including absorption profile, absorption rate, bioavailability (*f*) (as reflected in area under the concentration time curve [AUC]), and drug clearance. Some mean ± standard deviation parameters after food were as follows: maximum concentration of drug in serum (C_{max}), 443 ± 224 μg · liter^{-1}; time to C_{max}, 1.78 ± 1.2 h; AUC, 2,092 ± 1,441 ng · ml^{-1} · h, apparent clearance/*f*, 321 ± 167 liter · h^{-1}; mean residence time, 4.42 ± 1.31 h; and time at which half of the terminal value was reached, 0.97 ± 0.68 h. The total amount of artemisinin excreted in urine was less than 1% of the dose. We conclude that food intake has no major effect on artemisinin pharmacokinetics. In addition, we conclude tentatively that artemisinin is cleared by the liver, that this clearance does not depend on liver blood flow (i.e., that artemisinin is a so-called low-clearance drug), and that absorption of the drug is not affected by food intake.

Artemisinin and its derivatives are produced from the medicinal herb *Artemisia annua*. They constitute a class of potent antimalarial drugs. Some of these compounds have already been used for many years in areas in which malaria is endemic, mainly in Asia, and are currently undergoing phase II or phase III studies in other areas. Studies in China, Vietnam, and Thailand have shown that artemisinin and derivatives quickly reduce parasitemia in patients with acute falciparum malaria and induce fast resolution of symptoms (10, 11, 13, 17, 19, 22). Dosage regimens have largely been determined empirically. Few pharmacokinetic data are available to aid the development of rational dosage regimens, which is partly attributable to limited access to a sensitive and specific assay for measuring the concentration of artemisinin in plasma. A recently developed accurate high-performance liquid chromatography (HPLC) technique with electrochemical detection has now enabled additional studies (4, 12, 20).

In a previous study of the pharmacokinetics of artemisinin after a single 500-mg oral dose on an empty stomach in healthy Vietnamese subjects, it was found that absorption of artemisinin was rapid but probably incomplete, yielding peak concentrations of 289 to 734 ng · ml^{-1} (4). Very high values for the apparent volume of distribution/bioavailability ratio (*V*/*f*) and clearance/bioavailability ratio (Cl/*f*) were found. Mean ± standard deviation (SD) elimination was rapid, with a half-life of 2.6 ± 0.6 h.

The in vitro MIC of artemisinin for *Plasmodium falciparum* is 3 to 30 ng · ml^{-1} (8, 9, 18, 23). Plasma drug concentrations were higher than the MIC for up to 12 h after dosage. Since the bioavailability of artemisinin is probably low, influences on absorption might have implications for efficacy.

An important aspect of therapy is that artemisinin, a treatment for acute disease, will be administered irrespective of recent food intake. Artemisinin is neither very water soluble nor lipid soluble. Food intake could be a major determinant of absorption. Apart from its influence on absorption, food intake could also affect hepatic clearance by stimulation of liver blood flow, since hepatic clearance is probably the most important route of elimination for artemisinin (15, 16, 21). In view of these important clinical consequences, this study was performed to investigate the effects of food intake on the pharmacokinetics of artemisinin.

MATERIALS AND METHODS

Subjects. The study population consisted of six healthy Vietnamese male subjects. Their mean ± SD age was 29 ± 8 years, height was 164 ± 5 cm, weight was 48 ± 4 kg, body mass index was 1.8 ± 1.2 kg · m^{-2}, and body surface area was 1.5 ± 0.06 m^2. All volunteers gave written informed consent. Medical history and physical examination were normal for each volunteer. Values of routine laboratory tests including hemoglobin, hematocrit, leukocyte count, platelet count, blood urea nitrogen, creatinine, bilirubin, serum transaminases, and alkaline phosphatase were within normal limits, and hepatitis B surface antigen was not detectable. Electrocardiography results for all subjects were normal. A history of alcohol or drug abuse, recent use of medications, and known allergy to

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TABLE 1. Pharmacokinetic parameters of artemisinin in healthy subjects after a single oral 500-mg dose under fasting conditions

Subject	Result by:									
	Noncompartmental analysis						Compartmental analysis			
	AUC ($ng \cdot ml^{-1} \cdot h$)	$t_{1/2}$ (h)	Cl/*f* ($liters \cdot h^{-1}$)	*V*/*f* ($liters \cdot kg^{-1}$)	MRT (h)	MAT (h)[a]	T_{lag} (h)	T_{max} (h)	C_{max} ($ng \cdot ml^{-1}$)	MAT (h)[b]
1	2,647	1.89	188	10.6	3.60	0.81	0.97	1.17	1,056	0.05
2	786	2.16	635	33.3	3.59	0.78	0.0	2.49	211	1.25
3	1,849	2.22	270	18.4	4.55	2.62	0.99	4.0	377	1.51
4	2,444	2.4	204	13.7	3.80	0.71	0.76	1.60	620	0.41
5	4,300	2.61	116	9.3	5.45	2.0	0.56	4.96	749	2.20
6	3,652	3.79	136	13.2	5.25	1.1	0.85	1.75	724	0.36
Mean ± SD	2,611 ± 1,255	2.51 ± 0.67	258 ± 192	16.4 ± 8.8	4.39 ± 0.84	1.34 ± 0.79	0.69 ± 0.37	2.66 ± 1.50	623 ± 297	0.96 ± 0.83

[a] Calculated by the deconvolution technique.
[b] Calculated by nonlinear regression analysis.

artemisinin or one of its derivatives were exclusion criteria. For the entire study period, the subjects were admitted to the malaria unit of the Institute for Clinical Research in Tropical Medicine in Hanoi, Vietnam. The study protocol was approved by the Medical Ethics Committee of the Hospital of the University of Amsterdam, and institutional clearance was obtained from the Institute for Clinical Research in Tropical Medicine.

Drug administration and follow-up. On two consecutive days, two capsules of 250 mg of artemisinin (ACF Pharmaceuticals, Maarssen, The Netherlands) were administered with and without food in a crossover design after an overnight fast. The food consisted of a standard Vietnamese breakfast of approximately 400 ml of warm rice soup with some vegetables and meat. Three subjects (no. 1, 2, and 3) received artemisinin without food on the first day. They were allowed to eat 3 h after drug intake. The other subjects were studied in the reverse order. Subjective symptoms and vital signs (blood pressure, pulse rate, respiration rate, temperature, and consciousness) were recorded regularly, starting at hourly intervals. A complete physical examination was repeated 24 h after every drug administration.

Blood sampling and drug assay. For the pharmacokinetic studies, a total of 21 blood samplings were scheduled: just before intake of the first artemisinin capsules and at 1, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, and 24 h after each dose. The schedule was identical during the second day. From an indwelling intravenous catheter, 5-ml blood samples were drawn into vacuum polystyrene tubes (Venoject II; Terumo) containing lithium heparinate. The blood samples were centrifuged immediately, transferred to polypropylene tubes, and stored at −20°C. They were then transported to Amsterdam while frozen and stored there at −30°C until analysis. Urine was collected during the first 12 h after each dose. Samples of the two volumes of urine were stored and analyzed for artemisinin contents.

The HPLC assay used in this study was based on the assay of Melendez et al. with some modifications (20). In aggregate, the equipment consisted of a liquid chromatograph with a glassy carbon electrode, an autosampler (Gilson 222; Gilson Medical Electronics, Inc., Middleton, Wis.), and a diluter (Gilson 401). The column was prepacked with 10-μm-diameter particles with 125-Å pores (Versapack CN; 4.6 by 300 mm; Greenfield, Ill.). One milliliter of plasma was extracted by addition of 10 ml of *n*-butychloride–ethyl acetate (90:10). After being stirred and centrifuged at 4,000 rpm for 10 min, the sample was evaporated under nitrogen. Ethanol-water (1:1) was used for redissolution. Artemether was added as an internal standard (100 $\mu g \cdot ml^{-1}$ in 100% ethanol, redissolved to 10 $\mu g \cdot ml^{-1}$ in water-ethanol). The eluents consisted of acetonitrile at 20% in a buffer of sodium acetate and acetic acid at pH 5.0. One hundred microliters of the specimen was injected at a flow rate of 1.5 $ml \cdot min^{-1}$. The detection electrode was operated at −1.0 V and with a cutoff of background current of 100 mA. All glass materials were silanized before use. Following this procedure, the sensitivity of measurement of artemisinin concentrations is 10 ± 3 ng/ml at a signal/noise ratio of 3:1. All samples of one subject were analyzed one after another on the same day. A calibration line was constructed with four standard solutions before and after the assay of the samples of one subject. The calibration curves mostly showed negligible intercepts with very little variation of the slope and very small differences in the absolute values of the chromatogram readings. A mean correlation coefficient, *r*, of 0.997 of the calibration curves (minimum-to-maximum values of 0.992 to 0.999) was obtained during the assays. The coefficient of variation between the results of the two calibration procedures was always less than 5%.

Data analysis. All data analysis was done according to standard kinetic methodology as described by Gibaldi and Perrier (5). The elimination rate constant (k_{el}) was first estimated by log-linear regression of the straight terminal part of the curve; in all instances this was made up of the last four concentration time points. The elimination half-life ($t_{1/2el}$) was then calculated according to the formula $t_{1/2el} = \ln(2)/k_{el}$. The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule; extrapolation to infinity was done by addition of the quotient last concentration/k_{el}. Cl/*f* was then calculated as dose/AUC. *V* was calculated as (Cl/*f*)k_{el}. The additional kinetic parameters were calculated by three approaches: noncompartmental analysis by the method of statistical moments, a deconvolution technique, and nonlinear regression of the concentration-time curve.

The area under the statistical moments curve (AUMC) was calculated by multiplication of the concentration and time after dosage for all observations; the AUMC was then calculated by the trapezoidal rule, extrapolated to infinity by addition of the quotient last observation/k_{el}. The mean residence time (MRT) was calculated as AUMC/AUC.

A simple deconvolution approach was used to calculate absorption rates between successive plasma drug concentrations

$$\text{absorption rate} = [(C_{t_1} - C_{t_0} \cdot e^{-k_{el} \cdot (t_1 - t_0)}) \cdot V \cdot k_{el}]/(1 - e^{-k_{el} \cdot (t_1 - t_0)})$$

in which C_{t_1} and C_{t_0} and t_1 and t_0 are the concentrations and times, respectively, of two consecutive samples. From the absorption rates between successive time points, the cumulative amount of drug resorbed was calculated. MAT was estimated as the time at which half of the terminal value was reached by interpolation of the cumulative resorbed drug curve. Calculations were based on the assumption that there is 100% bioavailability, or in other words that $f = 1$.

Nonlinear regression was done with the computer program PCNONLIN (version 4.0; SCI Software, Lexington, Ky.). The concentration-time curves were fitted to a one-compartment first-order elimination model with a lag time. Equal weights were applied to all data points throughout all fittings. For the absorption phase, either a zero-order process (of variable duration) or a standard first-order absorption rate constant was incorporated in the model. Sums of squared deviations and Akaike's information criterion were used to compare the two approaches (25). In all instances, the input model defined as best by Akaike's information criterion corresponded with what was regarded the best fit based on visual inspection of the data. Time to 50% (MAT) absorption was calculated as 0.5 × absorption time for the zero-order absorption model and as $1/k_{abs}$ for the first-order model. The sum of MAT and the lag time (T_{lag}) should be compared to the MAT found by the deconvolution technique. The presented time to the maximum calculated concentration, T_{max}, includes T_{lag}, so that for zero-order absorption, $T_{max} = T_{lag}$ + absorption time.

Student's *t* test for paired observations was used to compare the experimental conditions.

RESULTS

The drug was tolerated well; no adverse reactions were observed during the experimental periods. The pharmacokinetic parameters after food are shown in Table 1, and those without food are shown in Table 2.

The log-linear concentration-time plot indicated the absence of a distribution phase. There were very large values for the parameters *V*/*f* and Cl/*f*. The deconvolution revealed two absorption profiles: one pattern was apparently first order (i.e., exponential), and the other was zero order (i.e., linear). The cumulative resorbed drug is shown in Fig. 1.

Fitting of the concentration-time curve to the one-compartment elimination model was successful for all subjects. For the description of most absorption phases, a lag time (T_{lag}) was

TABLE 2. Pharmacokinetic parameters of artemisinin in healthy subjects after a single oral 500-mg dose taken with food

Subject	Result by:									
	Noncompartmental analysis						Compartmental analysis			
	AUC ($ng \cdot ml^{-1} \cdot h$)	$t_{1/2}$ (h)	Cl/*f* ($liters \cdot h^{-1}$)	*V*/*f* ($liters \cdot kg^{-1}$)	MRT (h)	MAT (h)[a]	T_{lag} (h)	T_{max} (h)	C_{max} ($ng \cdot ml^{-1}$)	MAT (h)[b]
1	4,002	1.85	125	7.5	4.69	2.2	0.81	3.77	888	1.48
2	1,660	2.20	301	21.5	4.34	0.92	0.54	1.57	299	0.40
3	3,817	3.29	130	11.5	6.88	1.23	0.73	2.27	548	0.72
4	1,045	2.77	487	8.7	3.67	0.48	0.62	1.48	304	1.14
5	1,305	2.32	383	26.7	3.75	0.68	0.78	1.57	355	0.40
6	728	3.22	502	21.2	3.21	0.32	0.0	0.0	502	9.0
Mean ± SD	2,092 ± 1,441	2.61 ± 0.58	321 ± 167	16.2 ± 8.0	4.42 ± 1.31	0.97 ± 0.68	0.58 ± 0.30	1.78 ± 1.23	483 ± 224	0.69 ± 0.54

[a] Calculated by the deconvolution technique.
[b] Calculated by nonlinear regression analysis.

needed. Observed concentrations and the calculated concentration-time courses of two representative subjects (no. 1 with zero-order absorption and no. 6 with first-order absorption) are shown in Fig. 2. There was a fair agreement between parameters calculated with the compartmental and noncompartmental methods for every individual under both experimental conditions. Large interindividual variations among the pharmacokinetic parameters were found, resulting in large 95% confidence limits for the difference between parameters with food and those without food, which were as follows: AUC, −2,834 to 1,794 $ng \cdot ml^{-1} \cdot h$; $t_{1/2}$, −0.5 to 0.7 h; Cl/*f*, −232 to 359 $liters \cdot h^{-1}$; *V*/*f*, −11.6 to 11.1 $liters \cdot kg^{-1}$; MRT, −1.74 to 1.82 h; noncompartmental MAT, −1.18 to 0.97 h; T_{lag}, −0.59 to 0.38 h; T_{max}, −2.86 to 1.01 h; C_{max}, −376 to 100 $ng \cdot ml^{-1}$; and compartmental MAT, −0.96 to 1.5 h. The mean ± SD cumulative amounts of unchanged artemisinin excreted in urine over the first 12 h after drug administration were very small: 0.071 ± 0.053 mg with food and 0.033 ± 0.023 mg without food. The mean ± SD (minimum to maximum) time that the plasma drug concentration exceeded 30 $ng\ ml^{-1}$ (10^{-7} M), the upper range of what is reported as the MIC for *P. falciparum*, was 8.1 ± 4.1 (4.5 to 14.9) h for intake with food and 9.5 ± 2.6 (5.1 to 12.3) h without food. These values were not significantly different.

DISCUSSION

In this study, no adverse effects due to artemisinin were observed, which is compatible with extensive clinical experience indicating that artemisinin is a safe drug (1, 11).

There are reasons to suspect that food would have an influence on the pharmacokinetics of artemisinin. Artemisinin is poorly soluble in both water and oil. The milieu of the gastrointestinal tract is watery; this is changed by food intake, and thus a change in bioavailability might be anticipated. Moreover, food intake increases intestinal and liver blood flow (2). However, it is hard to predict the direction of possible changes on the basis of purely theoretical considerations and in vitro data. We did not observe a change in AUC (the parameter

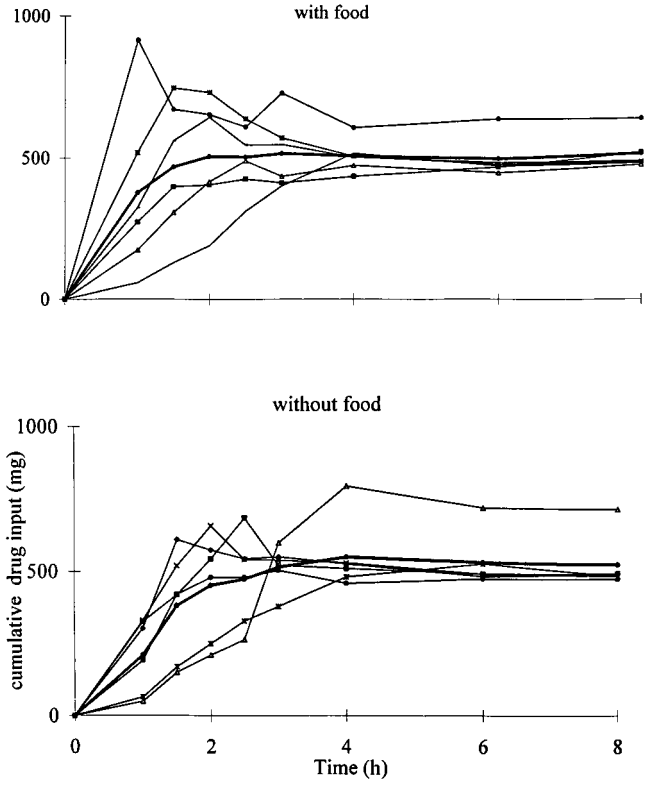

FIG. 1. Cumulative amount of artemisinin resorbed after administration with food and without food assuming 100% bioavailability. Curves were calculated by deconvolution (see text). Each symbol represents results for an individual patient.

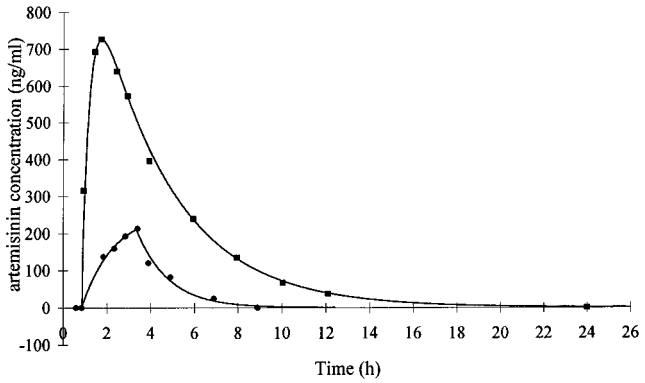

FIG. 2. Artemisinin concentrations and calculated concentration-time course of a one-compartment model with zero-order absorption (●) (data from subject no. 2 [artemisinin without food]) and with first-order absorption (■) (data from subject no. 6 [artemisinin without food]).

most likely to reflect bioavailability in our study design). It is thus unlikely that bioavailability is changed very much by food; this conclusion is strengthened by the fact that none of the other measures of absorption (e.g., absorption rate) shows a change after food intake.

Another important pharmacokinetic factor influenced by food is liver blood flow, and therefore bioavailability and/or systemic clearance (24). Because we found only trace amounts of unchanged artemisinin in urine, enzymatic, and thus most probably, hepatic, metabolism seems to the main route of elimination of artemisinin. Theoretically, biliary excretion is another possible route of elimination. The influence of changes in liver blood flow on pharmacokinetics depends on the relationship between liver blood flow and the intrinsic capacity of the liver to metabolize a drug (the so-called "intrinsic clearance") (14). When intrinsic clearance is high compared to liver blood flow, the rate-limiting factor in drug clearance is liver blood flow; changes in liver blood flow are thus expected to have an influence on pharmacokinetic parameters. When intrinsic clearance is low compared to liver blood flow, changes in liver blood flow do not affect clearance. Because we found no differences in the pharmacokinetics of artemisinin after food versus those before food, liver blood flow has no influence on the elimination or the bioavailability of artemisinin. Artemisinin is therefore probably a so-called low-clearance drug.

The very large V/f and Cl/f suggest that bioavailability is low. There is substantial accumulation in parasitized erythrocytes (6), and accumulation in other cells with a consequent large apparent V cannot be excluded. Full concentrations in blood cannot be measured accurately with HPLC. The difference between the AUCs on days 1 and 2 is not readily explained. A decrease in C_{max} during a multidose regimen was found recently by Hassan Alin et al. without a difference in elimination rate (7). Changing bioavailability was hypothesized. The increase in AUC in our six subjects cannot be explained easily; it should be stressed that the play of chance can have large effects in a study of six subjects.

The results of this study thus show that food intake probably has no substantial influence on the pharmacokinetics of orally administered artemisinin. Interindividual variation is large as is intraindividual variation. With poor bioavailability, small absolute changes of absorption have large relative effects. Because of the wide interindividual variation, the present study lacks the statistical power to detect small differences between the two experimental conditions. Such minor differences are of little practical consequence.

The single 500-mg dose of artemisinin has been shown to initiate a rapid decrease in parasites in patients with uncomplicated *P. falciparum* infections (3). It is not clear which kinetic parameter is the most significant determinant of therapeutic effect. Preliminary data show that at least peak concentrations should exceed the MIC. C_{max} was not affected by food intake. On the other hand, the time that the plasma drug concentration exceeds the MIC may also be significant. The 500-mg dose of artemisinin is sufficient to keep the plasma drug concentrations above the in vitro MIC for *P. falciparum* for 8 to 10 h. This time above the MIC is not affected by food.

In conclusion, the intake of food has no practical effects on the pharmacokinetics of oral artemisinin.

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